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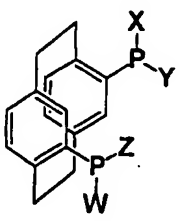
(54) Title: LIGANDS AND THEIR USE



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(57) Abstract: A compound of general formula 4 wherein each of W, X, Y and Z is any substituent where a heteroatom is bonded to phosphorus, optionally linked in pairs X/Y and Z/W to form a ring, or W=X=Y=Z=H, is new. Complexes thereof can be used in asymmetric reactions such as hydrogenation.

LIGANDS AND THEIR USE

Field of the Invention

This invention relates to new bidentate phosphines, phosphonite, phosphonous diamide and phosphonoamidite ligands having a *p*-cyclophane backbone, precursors thereof, and their use as ligands for transition metal-catalysed asymmetric reactions, notably rhodium, iridium and ruthenium-catalysed hydrogenation of double bonds.

Background of the Invention

At the heart of most asymmetric catalytic synthesis is the use of catalysts based on a transition metal surrounded by appropriate chiral, enantiomerically enriched, organic ligands. Bidentate chiral phosphines (phosphorus III compounds with three C-P bonds) are the most widely used class of ligands, finding applications in a range of asymmetric reactions (R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, **1994**; N. Jacobsen, A. Pfaltz, H. Yamamoto editors, *Comprehensive Asymmetric Catalysis*, Springer, **1999**). Asymmetric catalytic hydrogenation has a particular industrial relevance because of its high efficiency and reduced environmental impact.

It has recently been shown that some of the results obtained with phosphines-based catalysts can be matched by the use of complexes where the phosphane ligands have been replaced by phosphonites (two P-O bonds and one P-C bond, Reetz *et al*, *Chem. Commun.* **1998**, 2077), phosphine-phosphonites (Reetz *et al*, *Tetrahedron: Asymmetry* **1999**, 2129) or phosphoramidites (two P-N and one P-O bond, Feringa *et al*, *J. Am. Chem. Soc.* **2000**, 11539). Chiral monodentate phosphonites (Pringle *et al*, *Chem. Commun.* **2000**, 961; Reetz *et al*, *Tetrahedron Lett.* **2000**, 6333) and mono-phosphites (three P-O bonds, M.T. Reetz *et al*, *Angew. Chem. Int. Ed.* **2000**, 3889) were often as effective as the analogous bidentate ligands. The above ligands often have the advantage of being easier and cheaper to prepare than the corresponding diphosphines.

Chiral bidentate phosphonites are disclosed in WO-00/14096 and US-A-5817850. They are composed of three building blocks, i.e. an achiral carbon backbone (1,1'-disubstituted ferrocene, 1,2-disubstituted ethane) joining the two phosphorus atoms; and two chiral units derived from a chiral diol to form the P-heteroatom bonds. Examples of this class of ligands are described by Reetz *et al*, *Chem. Commun.* **1998**, 2077).

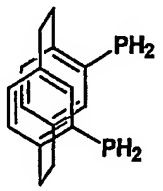
Some phosphorus diamide ligands have been reported, and their complexes have been demonstrated to be useful in hydroformilation reactions and allylic substitutions

(Wills *et al*, *J.Org.Chem.* **1999**, 9735; Spilling *et al. Tetrahedron* **1998**, *54*, 10513; *Tetrahedron: Asymmetry* **1998**, 927; Knochel *et al. Tetrahedron: Asymmetry* **1997**, 987).

[2.2]-*p*-Cyclophane derivatives bearing two identical substituents at so-called pseudo-*ortho* positions (4- and 12-positions; abbreviated as *ps-ortho*) possess planar chirality. The successful diphosphine ligand PhanePhos (Pye *et al*, *J. Am. Chem. Soc.* **1997**, 6207; WO 97/47632), is based on this skeleton.

Summary of the Invention

According to one aspect of the present invention, a novel compound is *ps-ortho*-diphosphino-[2.2]-*p*-cyclophane (**1**)

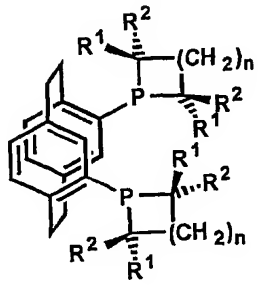


(1)

This compound is useful as a general intermediate that allows ready access to a range of cyclic phosphine ligands having application in asymmetric catalysis. Preferably, compound (**1**) is enriched to at least 80% ee in the enantiomer depicted (*S*) or in the opposite enantiomer (*R*). More preferably, it is enriched to 95% ee, or higher. Compound (**1**) may be prepared using the tetrachloro analogue described below as compound **4d**.

Further, it has now been appreciated that by combining the structural features of PhanePhos ligands (the chiral backbone) with either DuPHOS or FerroTANE ligands (phosphine atoms in 4- or 5-membered saturated ring) hybrid ligands represented by general formulae (**2**) and (**3**) can be envisaged, wherein R^1 and R^2 represent H or alkyl and n is 1 or 2. To date, no ligand of this type has been described in the literature. Importantly, the presence of a chiral backbone allows a flexible approach to ligand design, since the cyclic phosphine units may either be chiral (e.g. R^1 = methyl, R^2 = H or *vice versa*), allowing catalyst tuning through a "matched" diastereomeric pairing, or achiral (e.g. $R^1 = R^2$ =H), allowing construction from inexpensive diols of the type HO-$(CH_2)_n$-OH. It cannot be readily predicted which of ligands (**2**) and (**3**) will have industrial utility and, in order for this to be assessed systematically through screening experiments, the availability of a range of such ligands is required. To date, access to these ligands has been limited by

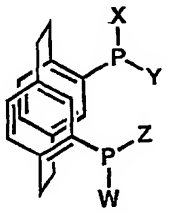
the non-availability of suitable precursors. Through the provision of compound (1), this limitation no longer applies.



(2) n = 1

(3) n = 2

According to another aspect, this invention is based on investigation of chiral phosphonites and phosphorus diamides, ligands having a chiral backbone. Based on the *ps-ortho* disubstituted [2.2]-*p*-cyclophane skeleton, a new class of molecules is of general formula **4**



X,Y,Z,W = O: **4a** *p*-cyclophane-phosphonites
X,Y,Z,W = N: **4b** *p*-cyclophane-phosphorus-amides
X,Z = O; Y,W = N: **4c** *p*-cyclophane-phosphonoamidite
X,Y,Z,W = Cl: **4d** bis(dichlorophosphino)-*p*-cyclophane
X,Y,Z,W = H: see formula 1

The most convenient synthesis of compounds **4a-c** is based on the reaction of *ps-ortho*-bis(dichlorophosphino)-*p*-cyclophane **4d** with the appropriate conjugate base pre-generated from a diol, diamine, amino-alcohol, alcohol or amine. Alternatively, compound **4d** can be reacted with the appropriate diol, diamine, alcohol or amine in the presence of stoichiometric or catalytic amounts of a suitable base, for example a tertiary amine. Compound **4d** can be obtained from the easily accessible precursor (*S*)-*ps-ortho*-dibromo-*p*-cyclophane (5) (D.J. Cram *et al, J. Am. Chem. Soc.* **1969**, 3527) *via* different synthetic routes.

The ease of preparation of compounds **4a-c** and the ready availability of the dioxo and diamido building blocks allows the generation of an unprecedented range of modifications based on the *p*-cyclophane backbone. In addition, the use of chiral chelating dialkoxo and di-amido substituents can enhance the chirality transfer in the catalytic process by means of a matching effect of the chirality of the backbone and the chirality of

the heteroatom units. The use of mono-dentate alkoxo and amido ligands produces more flexible ligands that can complement the more rigid and sterically congested dialkoxo/di-amido ligands. Chiral phosphonites derived from monodentate alcohols or amines are completely unprecedented.

Chiral di-phosphonites and phosphorus diamides based on the *ps-ortho* disubstituted *p*-cyclophane skeleton are good ligands for transition metals, notably rhodium, iridium and ruthenium. Compounds **6-8** are specific examples of the above mentioned complexes.

[(**4a-c**)Rh(COD)]BF_4	**6a-c**
[(**4a-c**)Ir(COD)]BF_4	**7a-c**
(**4a-c**)Ru(diamine)Cl_2	**8a-c**

Using the most bulky chiral dialkoxo substituents, a very strong matching/mismatching effect was found in the formation of the metal complexes. Complexes **6-8** act as highly efficient catalysts for asymmetric reactions, notably asymmetric hydrogenation. They may also be used for asymmetric hydroformylation.

In particular, high levels of stereoselection are induced by rhodium complexes **6a** of *p*-cyclophane phosphonites in the hydrogenation of dehydroaminoacids. These results match and in certain applications surpass the results reported for the known rhodium-phosphonites systems. Surprisingly, better results than in the literature are obtained in protic solvents; aprotic solvents give a noticeable increase in selectivity.

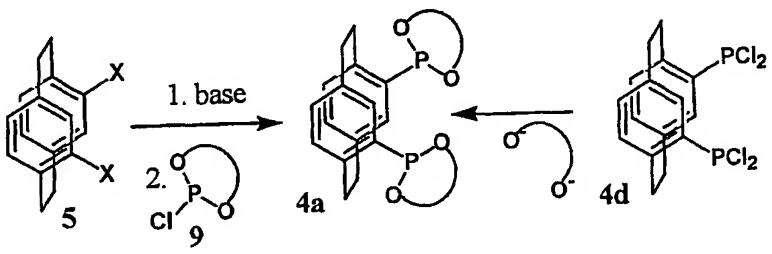
Further, the ruthenium complexes **8a** of *p*-cyclophane-phosphonite **4a** and a chiral diamine catalyse the reduction of non functionalised ketones and imines. While it is known that the reduction of ketones is catalysed by phosphine-ruthenium-diamine complexes (Noyori and Ohkuma, *Angew.Chem.Int.Ed.*, **2001**, 40), the results here presented are unprecedented.

Description of Preferred Embodiments

Compounds **4** of the invention may be prepared from enantiomerically pure *ps-ortho*-dihalogen-*p*-cyclophane **5** (X=Br). Phosphonites **4a** can be obtained by direct metalation of **5** with a strong organometallic base and reaction with the appropriate chloro-phosphonite **9** (Scheme 1). An alternative and more convenient procedure involves

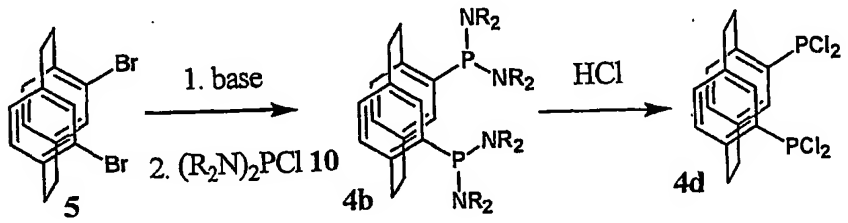
the reaction of the novel intermediate *ps-ortho*-bis(dichloro-phosphino)-*p*-cyclophane **4d** with the appropriate alcohol or diol or their metal bases (also in Scheme 1).

Scheme 1



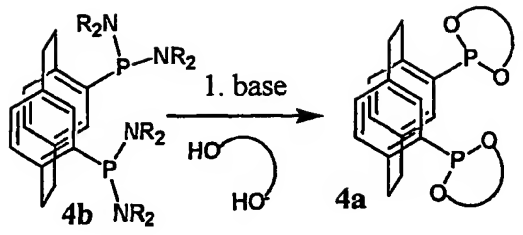
Compound **4d** was found to be a convenient general intermediate, easy to prepare and to handle. It is best prepared by metalating the dibromo compound **5** (X=Br), followed by quenching with a chloro-phosphorus-diamide **10** such as, for example, $ClP(NMe_2)_2$ or $ClP(i\text{-}Pr_2N)_2$ (Scheme 2). Compounds **4b** (R=Me, *i*-Pr) are transformed into compound **4d** by treating them with an HCl solution (Et_2O or any other convenient solvent), either generated *in situ* or preformed (again, see Scheme 2).

Scheme 2

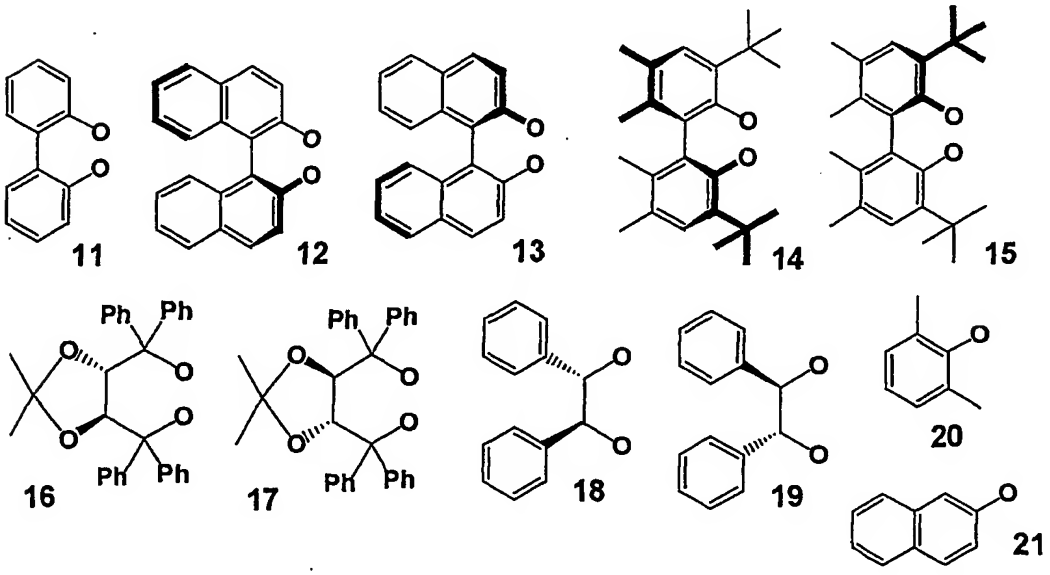


It is also possible to react compound **4b** (R=Me, *i*-Pr) directly with a diol in presence of an appropriate base to produce phosphonites **4a** (Buono *et al*, *Synlett* **1998**, 49; van Boom *et al*, *Tetrahedron Lett.* **2000**, 8635 - Scheme 3). The same procedure can be applied to the preparation of compounds **4b-c** by reaction with an appropriate diamine or aminoalcohol.

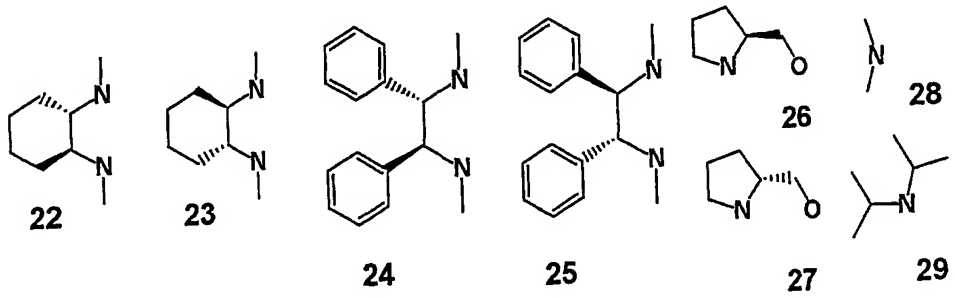
Scheme 3



It has been found that the reaction of **4d** with the conjugate base of a number of diols and alcohols proceeds smoothly at room temperature to provide the corresponding phosphonites **4a** in good yields. All of them are relatively insoluble in MeOH and can be isolated from the reaction crude simply by removing the reaction solvent and washing with MeOH (the salts generated in the reaction being soluble in MeOH). Specific examples of compounds **4a** are those were prepared from the alkoxo and di-alkoxo units **11-21**, of which **11**, **20** and **21** are achiral entities.



Examples of compounds **4b** and **4c** were prepared respectively from diamido units **22-25** and alkoxo-amido units **26-27**.



In compounds **4c**, the fact that the phosphorus atom becomes a stereogenic center might produce the formation of a mixture of diastereoisomers. Nevertheless, spectroscopic evidences indicate that phosphonoamidite **4c/23** is formed as single diastereoisomer (Example 13). Compounds **4b/28** and **4b/29** were prepared as precursors for the synthesis of key intermediate **5**. Compound **4d** is also a very convenient intermediate for the synthesis of the diphosphine **1**, by reduction with any of various reducing agents such as Red-Al or $LiAlH_4$.

Compounds **4a-c** were found to be good ligands for transition metals (notably rhodium, iridium, ruthenium). The metal complexes **6a-c**, **7a-c** and **8a-c** were generated according to standard procedures by reacting precursors such as $[(COD)_2Rh]BF_4$ and $[(COD)_2Ir]BF_4$, $[(benzene)RuCl_2]_2$. Other suitable metal-containing precursors can be used, according to the procedures known to those skilled in the art.

Unexpectedly, when phosphonites **4a/14** and **4a/15**, bearing the most bulky dialkoxo substituents are used, a very strong matching/mismatching effect is found in the formation of the metal complexes. Only the ligand derived from (*R*)-**15** and (*S*)-**4d** gave the desired Rh complex. The ligand derived from (*S*)-**14** and (*S*)-**4d** did not react with $[(COD)_2Rh]BF_4$. This allows the use of the ligand as a diastereoisomeric mixture, selectively forming the metal complex derived from the matching *(S)*-**4a**/*(R)*-**15** diasteroisomer. Conveniently a 1:1 mixture of **14** and **15** (racemic diol) may be used to prepare the said diastereoisomeric mixture. Alternatively, enantiomerically pure **14** or **15** can be combined with racemic **5**.

The rhodium complexes **6a** of phosphonites **4a** display high activity and selectivity in the hydrogenation of dehydroaminoacids. These results match any other result reported for the known rhodium-phosphonites systems. Surprisingly, better results than in the literature (Reetz *et al*, *Tetrahedron:Asymmetry* **1999**, 2129) are obtained in protic solvents (e.g. MeOH); the use of aprotic solvents (e.g. toluene) produces a slight increase in selectivity. The stability of the catalysts in protic solvents (e.g. MeOH or MeOH/H_2O) increases the potential utility in the hydrogenation of molecules of pharmaceutical interest, which are often polar and water-soluble molecules.

The ruthenium complexes **8a** containing ligands **4a** and a chiral diamine such as DPEN (1,2-diphenyl-1,2-ethanediamine) catalyse the reduction of non-functionalised ketones and imines. The asymmetric reduction of imines is particularly important since only a few catalysts are known to efficiently promote this transformation.

The following Examples illustrate the invention. Examples 1 to 14 show the synthesis of the ligand precursors and ligands (Examples 3 and 4 illustrate alternative procedures, to give the same product). Examples 15 and 16 show the synthesis of complexes. Examples 17 to 22 are of hydrogenation. Example 23 relates to compound **1**.

Example 1: *(S)-ps-ortho*-Bis[bis(dimethylamino)phosphino]-[2.2]-p-cyclophane (*S*)-**4b/28**

(S)-ps-ortho-Dibromo-*p*-cyclophane (1.098 g, 3 mmol) was placed in a Schlenk flask under nitrogen atmosphere and dissolved in anhydrous Et_2O (40 mL). The solution was then cooled to –78°C in a dry ice/ethanol bath. A pentane solution of *t*-BuLi (1.7 M, 7.1 mL, 12 mmol) was added dropwise over five minutes. The reaction was stirred at –78°C for 1 hour while $P(NMe_2)_3$ was placed in a Schlenk flask under nitrogen atmosphere and PCl_3 was slowly added at room temperature. The rate of addition was such that internal temperature did not raise above 30°C. The reaction was then diluted with anhydrous Et_2O (10 mL) and stirred at room temperature for 30 minutes. The *p*-cyclophane lithium dianion solution was removed from the cooling bath and immediately quenched with the solution of $ClP(NMe_2)_2$. The reaction was diluted with more Et_2O (15 mL) and allowed to reach room temperature over 30 minutes. Silica gel (~ 5 mL) was added and the reaction was stirred for further 20 minutes, then filtered over a sintered glass filter, under nitrogen atmosphere. The resulting clear colourless solution was evaporated under reduced pressure. The solid residue was redissolved in Et_2O (10 mL)

and added to MeOH (10 mL). Vacuum was applied to remove Et_2O and a white solid precipitated. The solid was allowed to settle and the supernatant solution was removed, the solid was washed with more MeOH (10 mL) and dried under vacuum (0.52 g, 39 % yield). The mother liquors were evaporated to dryness and the solid residue was treated as above with Et_2O (5 mL) and MeOH (5 mL) to produce a second crop of product (overall yield: 74%, white crystalline powder). ^{31}P NMR (162 MHz, C_6D_6): 120.3 ppm.

Example 2: (*S*)-*ps-ortho*-bis[bis(di-*i*-propylamino)phosphino]-[2.2]-*p*-cyclophane (*S*)-**4b/29**

(*S*)-*ps-ortho*-Dibromo-*p*-cyclophane (0.82 g, 2.24 mmol) was placed in a Schlenk flask under nitrogen atmosphere and dissolved in anhydrous Et_2O (30 mL). The solution was then cooled to –78°C in a dry ice/ethanol bath. A pentane solution of *t*-BuLi (1.7 M, 5.4 mL, 9.2 mmol) was added dropwise over five minutes. The reaction was stirred at –78°C for 10 minutes, then the cooling bath was removed and the reaction stirred for further 40 minutes. Solid $(i\text{-PrN})_2PCl$ (1.25 g, 4.68 mmol) was added in one portion and the reaction was stirred at room temperature for 30 minutes. Anhydrous MeOH (15 mL) was added, Et_2O was removed under reduced pressure. The white solid that precipitated out of solution was collected on a sinthered glass filter under nitrogen and dried under vacuum (1.26 g, 84% yield). ^{31}P NMR (162 MHz, C_6D_6): 86.1 ppm.

Example 3:(*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane (*S*)-**4d**

(*S*)-*ps-ortho*-bis[bis(dimethylamino)phosphino]-[2.2]-*p*-cyclophane (3.6 g, 8.1 mmol) was suspended in anhydrous Et_2O (300 mL). The suspension was cooled to –78°C in a dry ice/ethanol bath and anhydrous HCl was bubbled through the reaction to saturate it. The reaction was then allowed to warm up to room temperature over 1.5 hours. Nitrogen was bubbled through the reaction for 30 minutes. The salts were removed by filtration over a sintered glass filter under nitrogen. The solvent was evaporated; the solid white residue was washed with pentane (5 mL) and dried under vacuum to give the product as a white powder (2.07 g, 62% yield). ^{31}P NMR (162 MHz, $CDCl_3$): 169.2 ppm.

Example 4: (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane (*S*)-**4d**

A solution of HCl in Et_2O (2M, 50 mL, 100 mmol) was added to solid (*S*)-*ps-ortho*-bis[bis(di-*i*-propylamino)phosphino]-[2.2]-*p*-cyclophane (2.76 g, 4.12 mmol) at room temperature, under stirring. The reaction was stirred at room temperature for 18 hours, then the solvent was removed and the solid residue was suspended in Et_2O (50 mL).

Salts were removed by filtration. The solvent was removed, Et_2O (20 mL) and hexane (40 mL) were added and the resulting cloudy solution was filtered. The solvent was removed, hexane was added (60 mL), the reaction was heated to 70°C for 10 minutes, then the resulting cloudy solution was filtered to give a clear solution. The solvent was evaporated leaving the product as a white powder (0.95 g, 56% yield). ^{31}P NMR (162 MHz, $CDCl_3$): 169.2 ppm.

Example 5: (*S*)-*ps-ortho*-bis(5,7-6-phosphadibenzo[*a,c*]cyclohepten-6-yl)-[2.2]-*p*-cyclophane (*S*)-**4a/11**

n-BuLi (2.5 M in hexane, 1.64 mL, 4.1 mmol) was added to a solution of 2,2'-biphenol (373 mg, 2 mmol) in anhydrous THF (15 mL). The reaction was stirred for 40 minutes at room temperature, then the solution was added dropwise to a solution of (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (410 mg, 1 mmol) in anhydrous THF (20 mL). The reaction was stirred at room temperature for 1 hour, then it was quenched by adding MeOH (1mL). The solvent was removed under vacuum, anhydrous MeOH was added (10 mL). The resulting suspension was stirred for 10 minutes, then the solid was allowed to settle and the supernatant solution was removed. The procedure was repeated twice (2x 5 mL MeOH), then the white solid residue was dried under vaccum (438 mg, 69% yield).^{31}P NMR (162 MHz, $CDCl_3$): 194.2 ppm.

Example 6: (*S*)-*ps-ortho*-bis{(*R*)-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*']dinaphthalen-4-yl}-[2.2]-*p*-cyclophane (*S*)-**4a/13**

n-BuLi (2.5 M in hexane, 0.82 mL, 2.05 mmol) was added to a solution of (*R*)-BINOL (286 mg, 1 mmol) in anhydrous THF (10 mL). The reaction was stirred for 30 minutes at room temperature, then the solution was added dropwise to a solution of (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (205 mg, 0.5 mmol) in anhydrous THF (15 mL). The reaction was stirred at room temperature for 30 minutes, then it was quenched by adding MeOH (2 mL). The solvent was concentrated under vacuum to about 2 mL, then anhydrous MeOH was added (10 mL). The resulting suspension was stirred for 10 minutes, the solid was allowed to settle and the supernatant solution was removed. The solid was washed with more MeOH following the same procedure (5 mL MeOH), then the white solid residue was dried under vacuum (200 mg, 48% yield). ^{31}P NMR (162 MHz, C_6D_6): 217.6 ppm.

Example 7: (*S*)-*ps-ortho*-bis{(*S*)-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*']dinaphthalen-4-yl}-[2.2]-*p*-cyclophane (*S*)-**4a/12**

n-BuLi (2.5 M in hexane, 0.82 mL, 2.05 mmol) was added to a solution of (*S*)-BINOL (286 mg, 1 mmol) in anhydrous THF (10 mL). The reaction was stirred for 30 minutes at room temperature, then the solution was added dropwise to a solution of (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (205 mg, 0.5 mmol) in anhydrous THF (15 mL). The reaction was stirred at room temperature for 30 minutes, then it was quenched by adding MeOH (2 mL). The solvent was concentrated under vacuum to about 2 mL, then anhydrous MeOH was added (20 mL). The resulting suspension was stirred for 10 minutes, the solid was allowed to settle and the supernatant solution was removed. The white solid residue was dried under vacuum (300 mg, 72% yield). ^{31}P NMR (162 MHz, C_6D_6): 203.8 ppm.

Example 8: (*S*)-*ps-ortho*-bis{(*R*)-di-*t*-butyl-1,2,10,11-tetramethyl-5,7-dioxa-6-phospha-dibenzo[*a*,*c*]cyclohepten-6-yl}-[2.2]-*p*-cyclophane (*S*)-**4a/15**

n-BuLi (2.5 M in hexane, 0.82 mL, 2.05 mmol) was added to a solution of (*R*)-3,3'-*t*-butyl-5,5',6,6'-dimethyl-2,2'-biphenol (286 mg, 1 mmol) in anhydrous THF (10 mL). The reaction was stirred for 1 hour at 45°C minutes, then the solution was added dropwise over 40 minutes to a solution of (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (205 mg, 0.5 mmol) in anhydrous THF (20 mL) heated at 45°C. The reaction was stirred at 55°C for 1.5 hours, the solvent was concentrated under vacuum to about 2 mL, then anhydrous MeOH was added (10 mL). The resulting suspension was stirred for 10 minutes, the solid was allowed to settle and the supernatant solution was removed. The solid was washed with more MeOH following the same procedure (5 mL MeOH), then the white solid residue was dried under vacuum (257 mg, 53% yield). ^{31}P NMR (162 MHz, C_6D_6): 188.6 ppm.

Example 9: (*S*)-*ps-ortho*-bis((*S*)-di-*t*-butyl-1,2,10,11-tetramethyl-5,7-dioxa-6-phospha-dibenzo[a,c]cyclohepten-6-yl)-[2.2]-*p*-cyclophane (*S*)-**4a/14**

n-BuLi (2.5 M in hexane, 0.82 mL, 2.05 mmol) was added to a solution of (*S*)-3,3'-*t*-butyl-5,5',6,6'-dimethyl-2,2'-biphenol (355 mg, 1 mmol) in anhydrous THF (10 mL). The reaction was stirred for 1 hour at 30°C minutes, then the solution was added dropwise over 1 hour to a solution of (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (205 mg, 0.5 mmol) in anhydrous THF (20 mL) heated at 45°C. The

reaction was stirred at 55°C for 1 hour, the solvent was concentrated under vacuum to about 2 mL, then anhydrous MeOH was added (15 mL). The resulting suspension was stirred for 10 minutes, the solid was allowed to settle and the supernatant solution was removed. The solid was washed with more MeOH following the same procedure (2x15 mL MeOH), then the white solid residue was dried under vacuum (235 mg, 48% yield). ^{31}P NMR (162 MHz, C_6D_6): 180.9 ppm.

Example 10: *(S)-ps-ortho*-bis[di(2,6-dimethylphenoxy)-phosphino]-[2.2]-*p*-cyclophane *(S)*-**4a/20**

n-BuLi (2.5 M in hexane, 0.32 mL, 0.8 mmol) was added to a solution of 2,6-dimethylphenol (98 mg, 0.8 mmol) in anhydrous THF (5 mL). The reaction was stirred at room temperature for 15 minutes, then the solution was added to a solution of *(S)-ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (73 mg, 0.18 mmol) in anhydrous THF (5 mL). The reaction was stirred at room temperature for 30 minutes, then the solvent was evaporated. Et_2O (15 mL) and SiO_2 (~2 mL) were added and the reaction was filtered to get a clear solution. The solvent was concentrated to ~ 1mL and anhydrous MeOH (2 mL) was added. The resulting suspension was stirred for 10 minutes, the solid was allowed to settle and the supernatant solution was removed. The resulting white solid residue was dried under vacuum (yield not calculated). ^{31}P NMR (162 MHz, C_6D_6): 186.3 ppm.

Example 11: *(S)-ps-ortho*-bis[di(2-naphthoxy)phosphino]-[2.2]-*p*-cyclophane *(S)*-**4a/21**

(S)-ps-ortho-Dibromo-*p*-cyclophane (366 mg, 1 mmol) was placed in a Schlenk flask under nitrogen atmosphere and dissolved in anhydrous Et_2O (30 mL). The solution was then cooled to –78°C in a dry ice/ethanol bath. A pentane solution of *t*-BuLi (1.5 M, 2.75 mL, 4.1 mmol) was added dropwise. The cooling bath was removed and the reaction was allowed to warm up. After 30 minutes a solution of O,O'-bis(2-naphthyl)chlorophosphine (775 mg, 2.2 mmol) in Et_2O (10 mL) was added. The reaction was stirred at room temperature for further 90 minutes, then quenched with anhydrous MeOH (1 mL). The solvent was evaporated and the solid residue was re-dissolved in anhydrous Et_2O (10 mL) and MeOH (10 mL). The solvent was concentrated under reduced pressure to ~5 mL and the resulting white precipitate was allowed to settle. The supernatant solution was removed. The solid was washed with more MeOH (10 mL)

following the same procedure, then the white solid residue was dried under vacuum (275 mg, 33% yield). ^{31}P NMR (162 MHz, C_6D_6): 178.0 ppm.

Example 12: (S)-*ps-ortho*-bis{(4*S*,5*S*)-2,2-Dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]-dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-yl}-[2.2]-*p*-cyclophane (*S*)-**4a/16**

n-BuLi (2.5 M in hexane, 0.45mL, 1.1 mmol) was added to a solution of (4*S*,5*S*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (=TADDOL)(235 mg, 0.5 mmol) in anhydrous THF (4 mL). The reaction was stirred for 1 hour at room temperature, then the yellow solution was added dropwise over 1 min to a solution of (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (100 mg, 0.25 mmol) in anhydrous THF (5 mL) atroom temperature. The reaction was stirred at room temperature for 1 hour, the solvent concentrated to dryness under vacuum and anhydrous MeOH was added (3 mL). The resulting suspension was allowed to settle and the supernatant solution was removed. The solid was washed with more MeOH following the same procedure (3 mL) and the white solid residue was dried under vacuum (yield not calculated). ^{31}P NMR (162MHz, C_6D_6): 184.9.

Example 13: (*S*)-*ps-ortho*-bis{(*S*)-tetrahydropyrrolo[1,2-*c*][1,3,2]oxaphophol-1-yl}-*p*-cyclophane (*S*)-**4c/26**

n-BuLi (2.5 M in hexane, 0.84 mL, 2.1 mmol) was added to a solution of (S)-prolinol (106 mg, 1.05 mmol) in anhydrous THF (10 mL) at –78°C. The reaction was stirred at –78°C for 10 minutes, then the solution was added to a solution of (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (205 mg, 0.5 mmol) in anhydrous THF (10 mL). The reaction was stirred at room temperature for 1 hour, then the solvent was evaporated. Anhydrous THF (1 mL) and MeOH (15 mL) were added. The resulting suspension was stirred for 10 minutes, the solid was allowed to settle and the supernatant solution was removed. The solid was washed with more MeOH (5 mL) following the same procedure, then the white solid residue was dried under vacuum (100 mg, 45% yield). ^{31}P NMR (162 MHz, $CDCl_3$): 159.0 ppm.

Example 14: (S)-*ps-ortho*-bis{(4*R*,5*R*)-1,3-Dimethyloctahydrobenzo[1,3,2]diaza-phospholyl)-[2.2]-*p*-cyclophane (*S*)-**4b/23**

n-BuLi (2.5 M in hexane, 0.9mL, 2.3mmol) was added to a solution of (1*R*, 2*R*)-1,2-(*N*, *N'*-diaminomethylcyclohexane) (155 mg, 1.1 mmol) in anhydrous THF (6 mL) and the deep red solution was stirred for 1 hour at room temperature (precipitation of a red

solid was observed). A solution of (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane **4d** (210 mg, 0.5 mmol) in anhydrous THF (8 mL) was added to the previous suspension at room temperature. The reaction was stirred for 1 hour, the solvent concentrated to dryness under vacuum and anhydrous MeOH was added (5mL). The resulting suspension was allowed to settle and the supernatant solution was removed. The solid was washed with more MeOH following the same procedure (5 mL), then the pale yellow solid residue was dried under vacuum (yield not calculated). ^{31}P NMR (162MHz, C_6D_6): 132.4 ppm.

Example 15: General procedure for the synthesis of cationic rhodium complexes **6a**

Ligand **4a** (1.05 mmol) and $[(COD)_2Rh]BF_4$ (1 mmol) were dissolved in anhydrous DCM (5-10 mL) and the reaction was stirred at room temperature for 2-16 hours. The solvent was concentrated under vacuum to about 0.5 mL and anhydrous Et_2O (5-15 mL) was added. The resulting yellow suspension was stirred at room temperature for 10-30 minutes , the solid was allowed to settle and the supernatant solution was removed. The solid residue was washed following the same procedure with more Et_2O (2x 5mL) and dried under vacuum.

^{31}P NMR (162 MHz, $CDCl_3$): (*S*)-**6a/11**: 186.3 ppm (d), (*S*)-**6a/12**: 177.0 ppm (d), (*S*)-**6a/13**: 186.1 ppm (d), (*S*)-**6a/15**: 174.3 ppm (d), (*S*)-**6a/16**: 142.0 ppm (d).

Example 16: Ruthenium complexes **8a**

$[RuCl_2C_6H_6]_2$ (0.06 mmol) and ligand **4a** (0.11 mmol) were placed in a dry Schlenk flask under a nitrogen atmosphere. To the solids was added dry degassed DMF (1 mL) and the reaction vessel was evacuated and then repressurised with nitrogen gas. This was repeated four times. The Schlenk flask containing the heterogeneous mixture was placed in an oil bath at 100°C and stirring was applied for 3.5 hour. The homogeneous mixture was allowed to cool to room temperature and then (*R,R*)-DPEN (=1,2-diphenyl-1,2-ethanediamine) (0.12 mmol) was added. The mixture was stirred for 66 h at room temperature, then evaporated under high vacuum providing a solid. This was washed with dichlormethane (3 mL) and the solvent was evaporated. This process was repeated providing a tan-brown coloured powder.

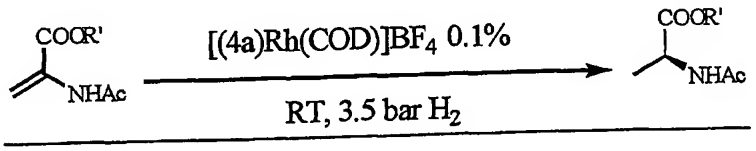
^{31}P NMR (162 MHz, $CDCl_3$): (*S*)-**8a/11**: 222.4 ppm; (*S*)-**8a/13**: 223.5 ppm.

Examples 17 to 20

All hydrogenations were carried out in a 50 mL Parr hydrogenation vessel equipped with an injection port with a rubber septum for the addition of the solvent using a syringe, a pressure gauge, a tightly fitting removable internal glass liner, a magnetic stirring bar. HPLC grade solvents ware degassed prior to the use by bubbling nitrogen for at least 30 minutes.

Substrate (2 mmol) and catalyst **6a** (0.002 mmol) were placed in the hydrogenation vessel that was subsequently closed and flushed with nitrogen. The vessel was purged with hydrogen by pressurising to 5 bar and then releasing the pressure. This procedure was repeated at least four times. The solvent (5 mL) was added through the injection port and the reaction was purged again with hydrogen. It was then pressurised to 3.5 bar and stirred at room temperature. The reaction was stopped when no more hydrogen uptake was detected on the pressure gauge. A crude reaction sample was diluted in MTBE and analysed by GC (DexCB chiral column, the free acid was derivatised by adding an excess of trimethylsilyl diazomethane) for conversion and selectivity.

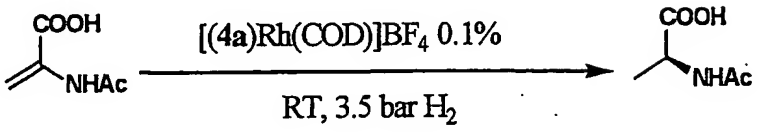
Example 17: Hydrogenation of methyl acetamidoacrylate



Catalyst	Diol component of the ligand	Solvent	Time (h)	Conv. (%)	Ee (%)
(*S*)-**6a/11**	biphenol	MeOH	0.5	> 99	89 (*S*)
(*S*)-**6a/13**	(*R*)-BINOL	MeOH	0.5	> 99	99 (*S*)
(*S*)-**6a/12**	(*S*)-BINOL	MeOH	1	~ 2	-
(*S*)-**6a/12**	(*S*)-BINOL	MeOH	16	98	74 (*S*)
(*S*)-**6a/15**	(*R*)-BIPHEN	MeOH	21	25	46 (*S*)
(*S*)-**6a/11**	biphenol	MeOH/H_2O 9/1	3	> 99	96 (*S*)
(*S*)-**6a/11**	biphenol	DCM	1	> 99	98 (*S*)
(*S*)-**6a/11**	biphenol	Toluene	0.5	> 99	99 (*S*)
(*S*)-**6a/21**	naphthol*	MeOH	15	>99	37 (*R*)
(*S*)-**6a/21**	naphthol*	Toluene	15	80	31 (*R*)

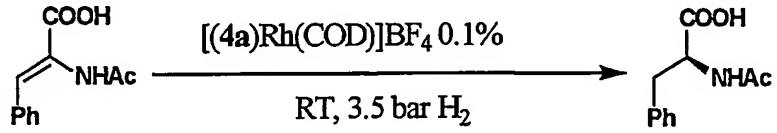
*monodentate component

Example 18: Hydrogenation of acetamidoacrylic acid



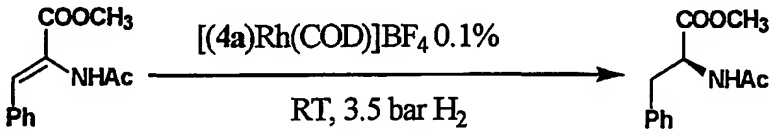
Catalyst	Diol component of the ligand	Solvent	Time (h)	Conv. (%)	Ee (%)
(*S*)-**6a/13**	(*R*)-BINOL	MeOH	0.5	> 99	97 (*S*)

Example 19: Hydrogenation of acetamidocinnamic acid



Catalyst	Diol component of the ligand	Solvent	Time (h)	Conv. (%)	Ee (%)
(*S*)-**6a/11**	biphenol	MeOH	0.5	> 99	93
(*S*)-**6a/13**	(*R*)-BINOL	MeOH	0.5	> 99	99

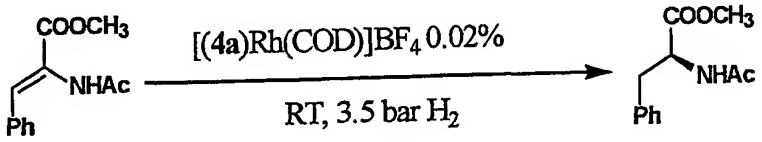
Example 20: Hydrogenation of methyl acetamidocinnamate



Catalyst	Diol component of the ligand	Solvent	Time (h)	Conv. (%)	Ee (%)
(*S*)-**6a/11**	biphenol	MeOH	0.5	> 99	95 (*S*)
(*S*)-**6a/13**	(*R*)-BINOL	MeOH	0.5	> 99	97 (*S*)
(*S*)-**6a/13**	(*R*)-BINOL	toluene	2	> 99	99 (*S*)

Example 21: Hydrogenation of methyl acetamidocinnamate at reduced catalyst loadings

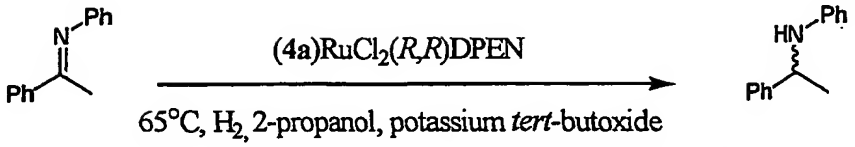
Substrate (10 mmol) and catalyst **6a** (0.002 mmol) were placed in the hydrogenation vessel that was subsequently closed and purged with nitrogen by pressurising to 5 bar and releasing the pressure. The procedure was repeated three times. The vessel was subsequently purged with hydrogen by pressurising to 5 bar and then releasing the pressure. This procedure was repeated at least four times. The solvent (5 mL) was added through the injection port and the reaction was purged again with hydrogen. It was then pressurised to 5 bar and stirred at room temperature. The reaction was refilled with hydrogen in order to maintain the pressure between 5 and 3.5 bar. The reaction was stopped when no more hydrogen uptake was detected on the pressure gauge. A crude reaction sample was diluted in MTBE and analysed by ^1H NMR for conversion and by GC (DexCB chiral column) for selectivity.



Catalyst	Diol component of the ligand	Solvent	Time (h)	Conv. (%)	Ee (%)
(*S*)-**6a/11**	biphenol	MeOH	0.5	> 99	95 (*S*)
(*S*)-**6a/13**	(*R*)-BINOL	MeOH	0.5	> 99	98.5 (*S*)

Example 22: imine hydrogenation with catalyst **8a**

N-(1-Phenylethylidene)aniline (1 mmol) and the catalyst were placed in the hydrogenation vessel that was subsequently closed and flushed with nitrogen. The vessel was purged with hydrogen by pressurising to 20 bar and then releasing the pressure. This procedure was repeated at least four times. 2-Propanol (4 mL) was added through the injection port and the reaction was purged again with hydrogen five times. The pressure was released and 1 M potassium *tert*-butoxide in *tert*-butanol (0.1 mmol) was added and the reaction was purged again with hydrogen four times. The reaction was pressurised to 15 bar and stirred at 65°C for 20.5 h. A crude reaction sample was diluted in acetone and analysed by GC (DexCB chiral column) for conversion and selectivity.



Catalyst (amount)	Diol component of the ligand	Equivalents *t*-BuOK	Pressure (bar)	Time (h)	Conv. (%)	Ee (%)
(*S*)-**8a/11** (1%)	biphenol	0.1	15	20.5	88	62
(*S*)-**8a/11** (1%)	biphenol	1	15	20	91	64
(*S*)-**8a/11** (0.1%)	biphenol	0.1	20	69	100	72

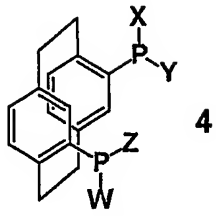
Example 23: (*S*)-*ps-ortho*-Diphosphino-[2.2]-*p*-cyclophane **1**

Method A: A 100mL Schlenck flask equipped with a stirring bar was dried with heating and then filled with nitrogen. To this was added (*S*)-*ps-ortho*-bis(dichlorophosphino)-[2.2]-*p*-cyclophane (**4d**, Example 4: 300mg, 0.75g) and dry, degassed toluene (4mL). The resulting solution was put in an oil bath at 50°C and allowed to stabilize at that temperature for 5 min. A solution of Red-Al (65%wt solution in toluene, 1.9 mL, 8.0 mmol) was added over 2 min. The solution, which rapidly turned red, was well stirred for 2hrs. After cooling down to room temperature, aqueous hydrochloric acid (2M, 5mL) was slowly added, whereby vigorous gas evolution was observed. The upper, organic layer was transferred *via* cannula to a similarly dried 100mL Schlenck flask equipped with a stirring bar. The aqueous phase is further extracted with toluene (2 x 4mL) and transferred to the second Schlenck flask. The mixed organic layers are evaporated to dryness under reduced pressure with gentle heating to furnish a yellow oil comprising mainly the desired product; ^{1}H NMR (400 MHz, C_6D_6): 2.3-2.7 (m, 3H); 3.0-3.1 (m, 1H); 3.55 and 3.75 (2d, ^1J = 200, ^2J = 12.6, 2H); 6.7-7.0 (m, 3H); ^{31}P NMR (162 MHz, C_6D_6): -113.4 (t of d, ^1J = 200, ^3J = 7.9).

Method B: A solution of *ps-ortho*-bis(dichlorophosphino)-[2,2]-*p*-paracyclophane (**4d**, 1.5 g, 3.65 mmol) in anhydrous THF (6 mL) was cooled to 0°C. A solution of $LiAlH_4$ in Et_2O (1M, 30 mL, 30 mmol) was added at 0°C and the reaction mixture was stirred for 30 hours and allowed to reach room temperature during this time. It was then cooled again to 0°C and degassed H_2O (3 mL) was added dropwise over 1 hour. The reaction mixture was evaporated to dryness under reduced pressure and the solid residue triturated with CH_2Cl_2, 5 mL x 3). The solvent was removed under reduced pressure to give the product as a yellow solid (0.76 g, 76% yield).

CLAIMS

1. A compound of general formula **4**



4

wherein each of W, X, Y and Z is any substituent where a heteroatom is bonded to phosphorus, optionally linked in pairs X/Y and Z/W to form a ring, or W=X=Y=Z=H.

2. A compound according to claim 1, wherein the pair of substituents X/Y is the same as pair Z/W.

3. A compound according to claim 1 or claim 2, wherein W, X, Y and Z each include a heteroatom selected from halogen, nitrogen, oxygen or sulphur.

4. A compound according to claim 3, wherein the heteroatom is oxygen.

5. A compound according to claim 4, wherein the pairs of substituents X/Y and Z/W are each the conjugate base of a diol.

6. A compound according to claim 3, wherein the heteroatom is nitrogen.

7. A compound according to claim 6, wherein the pairs of substituents X/Y and Z/W are each the conjugate base of a primary or secondary diamine.

8. A compound according to claim 3, wherein in each pair of substituents X/Y and Z/W the heteroatoms are oxygen and nitrogen.

9. A compound according to claim 8, wherein the pairs of substituents X/Y and Z/W are each the conjugate base of an aminoalcohol.

10. A compound according to any preceding claim, which is chiral and enantiomerically enriched.

11. A compound according to claim 5, wherein the diol is an enantiomerically enriched chiral diol.

12. A compound according to claim 11, wherein the chiral diol is a biaryl diol with axial chirality.

13. A compound according to claim 9, wherein the diamine is an enantiomerically enriched chiral primary or secondary diamine.

14. A compound according to claim 9, wherein the aminoalcohol is an enantiomerically enriched chiral aminoalcohol.

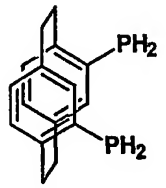
15. A compound according to any of claims 10 to 14, wherein the ee is at least 80%.

16. A compound according to claim 15, wherein the ee is at least 90%.

17. A compound according to claim 5, wherein the diol is achiral.

18. A compound according to claim 1, wherein X=Y=Z=W=Cl.

19. A compound according to claim 1, which is *ps-ortho*-diphosphino-[2.2]-*p*-cyclophane (**1**)



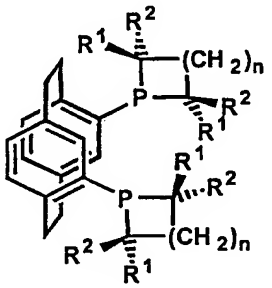
(1)

20. The compound according to claim 19, in enantiomerically enriched form.

21. The compound according to claim 20, in at least 80% ee.

22. The compound according to claim 20, in at least 95% ee.

23. Use of a compound according to any of claims 19 to 22, for the preparation of a chiral ligand (**2**) or (**3**)



wherein R^1 and R^2 represent H or alkyl and n is 1 (**2**) or 2 (**3**).

24. A complex of an enantiomerically enriched compound according to any of claims 10 to 17, a transition metal, and any other neutral ligand and counterion necessary to complete the coordination sphere of the metal.

25. A complex according to claim 24, wherein the transition metal is rhodium, iridium or ruthenium.

26. A complex according to claim 24 or claim 25, wherein the ligand is as defined in any of claims 5, 11 and 12.

27. A complex according to claim 24 or claim 25, wherein the ligand is as defined in any of claims 6, 7 and 13.

28. A complex according to claim 24 or claim 25, wherein the ligand is as defined in any of claims 8, 9 and 14.

29. A complex according to claim 26, of the formula

[(ligand)(diene)metal]Q

wherein the metal is rhodium or iridium, the diene is COD or NBD, and Q is BF_4 or PF_6.

30. A complex according to claim 29, wherein the metal is rhodium, the diene is COD, and Q is BF_4.

31. A complex according to claim 29, wherein the metal is iridium, the diene is COD, and Q is BF_4.

32. A complex according to claim 26, of the formula

[(ligand)(diamine)metal(hal)$_2$]

wherein the metal is ruthenium, hal is a halogen atom, and the diamine is an enantiomerically enriched chiral diamine.

33. A method for the preparation of a compound according to any of claims 5, 11, 12 and 17, which comprises reacting a compound according to claim 3 with the conjugate base of an alcohol or a diol.

34. A method for the preparation of a compound according to any of claims 6, 7 and 13, which comprises reacting a compound according to claim 3 with the conjugate base of an amine or diamine.

35. A method for the preparation of a compound according to any of claims 8, 9 and 14, which comprises reacting a compound according to claim 3 with the conjugate base of an aminoalcohol.

36. Use of a complex according to any of claims 24 to 32, to catalyse an asymmetric process.

37. Use according to claim 36, wherein the asymmetric process is hydrogenation.

38. Use according to claim 37, wherein the hydrogenation is of a C=C, C=N or C=O double bond.

39. Use according to claim 37, wherein the complex is according to claim 25.

40. Use according to claim 39, wherein the complex is according to claim 29.

41. Use according to claim 37, wherein the hydrogenation is of a C=N or C=O double bond and the complex is according to claim 32.

42. Use according to claim 36, wherein the asymmetric process is hydroformylation.

INTERNATIONAL SEARCH REPORT

In...ional Application No
PCT/GB 02/00219

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/48 C07F9/52 C07F9/50 C07F9/6571 C07F9/6584
C07F9/6568 C07F15/00 C07B53/00 C07C45/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F C07B C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 47632 A (MERCK & CO., INC.) 18 December 1997 (1997-12-18) cited in the application the whole document ---	1-42
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2002	04/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Beslier, L

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/00219

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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